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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,731	03/04/2005	Nicole Francisca Johanna Van Poppel	I-2002-017 US	5787

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INTERVET INC.
PATENT DEPARTMENT
PO BOX 318
MILLSBORO, DE 19966-0318

EXAMINER	
HINES, JANA A	
ART UNIT	PAPER NUMBER
1645	

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10/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,731	VAN POPPEL ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-38* is/are pending in the application.

4a) Of the above claim(s) *36-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/4/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I in the reply filed on August 22, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on March 4, 2005 was filed. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code such as (http://www.ncbi.nlm.nih.gov) on page 6, lines 17. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

4. Claims 33 and 35 are objected to because of the following informalities: Claims 33 and 35 are dependent upon claim 1, however claim 1 has been cancelled. Therefore, appropriate correction of claim dependency is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 34-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

Claim 34 is drawn to a vaccine for combating parasitic infection comprising the attenuated live parasite and a pharmaceutically acceptable carrier. Claim 35 is drawn to a method for the production of the vaccine, said method comprising the mixing of a live attenuated parasite and a pharmaceutically acceptable carrier.

The instant specification fails to provide any experiments that show that such vaccines would be effective in protecting a human or other animal against a gram-negative bacterial infection. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to any type of infection or disease induction. The vaccine art is highly unpredictable and the instant specification fails to provide any information that the recited attenuated live parasite vaccine would provide any immunity to any type of patient against any type of infection. There are still no immunological experiments provided to demonstrate that the claimed vaccines are capable of mounting an effective immune response. More importantly, there are no challenge

experiments to demonstrate that an animal immunized with the claimed parasite that would be protected from any parasitic infection.

There are no protocols provided which demonstrate which parasite would be effective in immunization, nor are their protocols detailing the amount of parasite needed to mount a sufficient immune response. There is no teaching as to what the most effective route of administration for the claimed vaccines. There is merely a general outline of vaccines that do not apply directly to the instant invention. The claims and specification fail to disclose the type of vaccine or components that should be administered to a subject. Therefore the specification fails to provide support for the claims. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of combating parasitic infections. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced against a parasitic infection. The specification fails to teach the identity a vaccine with the claimed characteristics. Furthermore, the specification fails to adequately disclose a description of the claimed vaccines, thus a skilled artisan would be required to de novo locate, identify and characterize the claimed vaccines with the recited abilities. Accordingly, this would require undue experimentation given the fact that the specification is completely lacking in teachings as to attenuated live vaccines with the broadly claimed protection characteristics. Thus, the art indicates that it would require undue experimentation to

formulate and use a successful attenuated live vaccine without the prior demonstration of vaccine efficacy.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 21, 28-32 and 34-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Wirtz et al., (1999. Molecular and Biochem. Parasit. Vol. 99: 89-101).

Claim 21 is drawn to an attenuated live parasite of the phylum Apicomplexa, wherein said parasite comprises a ribosomal protein gene under the control of an inducible promoter. Claim 28 is drawn to the attenuated live parasite, wherein said parasite belongs to the genus Trypanosoma. Claim 29 is drawn to the attenuated live parasite, wherein said inducible promoter is based upon an operator site and a repressor protein capable of reversibly binding said operator site. Claim 30 is drawn to the attenuated live parasite, wherein said inducible promoter is inducible by antibiotics. Claim 31 is drawn to the attenuated live parasite, wherein said inducible promoter is inducible by tetracycline. Claim 32 is drawn to the attenuated live parasite, wherein a tetR-system is used as the inducible promoter. Claim 34 is drawn to a vaccine for combating parasitic infection comprising the attenuated live parasite and a

pharmaceutically acceptable carrier. Claim 35 is drawn to a method for the production of the vaccine, wherein said method comprises mixing of a live attenuated parasite and a pharmaceutically acceptable carrier.

Wirtz et al., teach the inducible expression of transgenes in Trypanosome mediated by the Tet repressor (tetR) inserted in the PARP promoter (page 89). Wirtz et al., teach the promoter was responsive to the antibiotic tetracycline (page 90). Wirtz et al., teach conditional gene knockouts while disrupting native alleles thereby providing the attenuated live parasite (page 90) Wirtz et al., teach the generation of transgenic bloodstream-form cell-lines suspended in cytomix, thereby providing for the parasite and a pharmaceutically acceptable carrier (page 93).

Therefore Wirtz et al., teach the inventions as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 21-27 and 29-31 rejected under 35 U.S.C. 103(a) as being unpatentable over Sutherland et al., (1996. Experimental Parasitol. Vol. 83 :125-133) in view of Xu et al., (WO 98/37185).

Claim 21 is drawn to an attenuated live parasite of the phylum Apicomplexa, wherein said parasite comprises a ribosomal protein gene under the control of an

inducible promoter. Claim 22 is drawn to the attenuated live parasite according to Claim 21, wherein said parasite belongs to the *Coccidia*, the *Piroplasmida* or the *Haemosporida*. Claim 23 is drawn to the attenuated live parasite, wherein said parasite belongs to the family of the *Eimeridiidae, Cryptosporidiidae* or *Sarcocystidae*. Claim 24 is drawn to the attenuated live parasite, wherein said parasite belongs to the genus *Eimeria, Cryptosporidium, Toxoplasma, Sarcocystis* or *Neospora*. Claim 25 is drawn to the attenuated live parasite, wherein said parasite belongs to the family of the *Babesiidae* or the *Theileriidae*. Claim 26 is drawn the attenuated live parasite, wherein said parasite belongs to the genus *Babesia* or *Theileria*. Claim 27 is drawn to the attenuated live parasite, wherein said parasite belongs to the genus Plasmodium. Claim 29 is drawn to the attenuated live parasite, wherein said inducible promoter is based upon an operator site and a repressor protein capable of reversibly binding said operator site. Claim 30 is drawn to the attenuated live parasite, wherein said inducible promoter is inducible by antibiotics. Claim 31 is drawn to the attenuated live parasite, wherein said inducible promoter is inducible by tetracycline.

Sutherland et al., teach the attenuation of *Theileria* cell lines will afford protection from challenges and have been used for the development of live attenuated vaccines (page 125, col. 2). Sutherland et al., teach the selection of other avirulent apicomplexan protozoa which have resulted in reduced virulence (page 126, col.1). Sutherland et al., teach live attenuated *Babesia* and *Plasmodium* vaccines (page 126, col.1). Sutherland et al., teach desire and need to control gene expression in such parasites. However

Sutherland et al., do not teach the parasites comprises a ribosomal protein gene under the control of an inducible promoter.

Xu et al., teach the expression of genes whose products have a harmful effect and the desire and need to control gene expression in a wide variety of expression systems (page 2, lines 29-31). Xu et al., teach a number of prokaryotic expression vectors that provide controlled gene expression (page 2, lines 31-32). Xu et al., teach inducible expression vectors which relies on tightly regulated tetracycline responsive promoters which represent a significant advance in the art (page 3, lines 5-20).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply the attenuated live parasite of Sutherland et al., which incorporates a ribosomal protein gene under the control of an inducible promoter as taught by Xu et al., in order to provide a significant advance in the art. One of ordinary skill in the art would have a reasonable expectation of success by incorporating the ribosomal protein gene under the control of an inducible promoter because Xu et al., teach that an inducible system advantageously provides stringent regulation of gene expression in prokaryotes, thereby requiring the use of smaller amounts of tetracycline in order to function effectively. Furthermore, no more than routine skill would have been required to incorporate the ribosomal protein gene under the control of an inducible promoter since Xu et al., teach the expression of genes whose products have a harmful effect and the desire and need to control gene expression in a wide variety of expression systems by incorporating a ribosomal protein gene under the control of an inducible promoter.

Finally it would have been prima facie obvious to combine the invention of Sutherland et al., and Xu et al., to advantageously achieve a less toxic live attenuated prokaryotic cell line.

8. Claims 21, 28-32 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Titus et al., (1995. PNAS, Microbio. Vol. 92:10267-10271) in view of Yan et al., (2001. Mol. & Biocchem. Parasitol. Vol.112 :61-69).

Claim 21 is drawn to an attenuated live parasite of the phylum Apicomplexa, wherein said parasite comprises a ribosomal protein gene under the control of an inducible promoter. Claim 28 is drawn to the attenuated live parasite, wherein said parasite belongs to the genus Leishmania. Claim 29 is drawn to the attenuated live parasite, wherein said inducible promoter is based upon an operator site and a repressor protein capable of reversibly binding said operator site. Claim 30 is drawn to the attenuated live parasite, wherein said inducible promoter is inducible by antibiotics. Claim 31 is drawn to the attenuated live parasite, wherein said inducible promoter is inducible by tetracycline. Claim 32 is drawn to the attenuated live parasite, wherein a tetR-system is used as the inducible promoter. Claim 34 is drawn to a vaccine for combating parasitic infection comprising the attenuated live parasite and a pharmaceutically acceptable carrier. Claim 35 is drawn to a method for the production of the vaccine, wherein said method comprises mixing of a live attenuated parasite and a pharmaceutically acceptable carrier.

Titus et al., teach the development of a safe live attenuated *Leishmania* vaccine by gene replacement (page 10267). Titus et al., teach the use of live *Leishmania* would provide a superior vaccine (page 10267). However Titus et al., do not teach *Leishmania* comprising a ribosomal protein gene under the control of an inducible promoter.

Yan et al., teach tetracycline regulated gene expression in Leishmania (page 61). Yan et al., teach that conventional gene replacements strategies are unlikely to be useful (page 61). Therefore, Yan et al., teach an inducible system that provides stringent regulation of gene expression in Leishmania while offering great advantages (page 61). Yan et al., teach that the tetracycline-responsive repressor/operator system is tighter with the consequence that much lower amounts of tetracycline are needed in order to function effectively (page 61-62). Yan et al., teach that the inducer TetR binds to TetO operator and suppresses transcription from the adjacent promoter (page 62). Yan et al., teach the promoter placement in reverse orientation relative to the rDNA transcription locus (page 66). Yan et al., teach that current options for disease control are limited and more effective, less toxic protective vaccines are needed to manage the disease (page 61).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply the attenuated live parasite of Titus et al., which incorporates a ribosomal protein gene under the control of an inducible promoter as taught by Yan et al., in order to provide more effective protective *Leishmania* vaccines. One of ordinary skill in the art would have a reasonable expectation of success by incorporating the

ribosomal protein gene under the control of an inducible promoter because Yan et al., teach that an inducible system advantageously provides stringent regulation of gene expression in *Leishmania*, thereby allowing much lower amounts of tetracycline in order to function effectively. Furthermore, no more than routine skill would have been required to incorporate the ribosomal protein gene under the control of an inducible promoter since Yan et al., teach that conventional gene replacements strategies are unlikely to be useful in the production of stable live attenuated cell lines. Finally it would have been prima facie obvious to combine the invention of Titus et al., and Yan et al., to advantageously achieve less toxic protective vaccines that manage *Leishmania* infections.

Conclusion

9. No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Bruce Campell, can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
October 25, 2007

MARK NAVARRO
PRIMARY EXAMINER